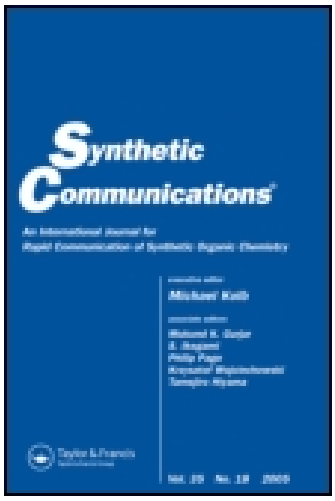

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STUDIES ON THE DIASTEREO- SELECTIVE REDUCTION OF 2-ACETYL-2-ALKYL- γ-BUTYROLACTONES WITH BORON HYDRIDES*

Lis H. P. Teixeira [a] , Maria Cecília B. V. de Souza [b] , Maria da Conceição K. V. Ramos [a] , Francisco R. de Aquino Neto [a] , Eliezer J. Barreiro [a] & Carlos A. M. Fraga [c]

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STUDIES ON THE DIASTEREOSELECTIVE REDUCTION OF 2-ACETYL-2-ALKYL-γ-BUTYROLACTONES WITH BORON HYDRIDES*

Lis H. P. Teixeira,[1] Maria Cecília B. V. de Souza,[2] Maria da Conceição K. V. Ramos,[3] Francisco R. de Aquino Neto,[3] Eliezer J. Barreiro,[1] and Carlos A. M. Fraga[1,†]

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ABSTRACT

Reduction of 2-acetyl-2-alkyl-γ-butyrolactone derivatives with boron hydrides in the presence and absence of several

*This paper is the contribution #53 from LASSBio.
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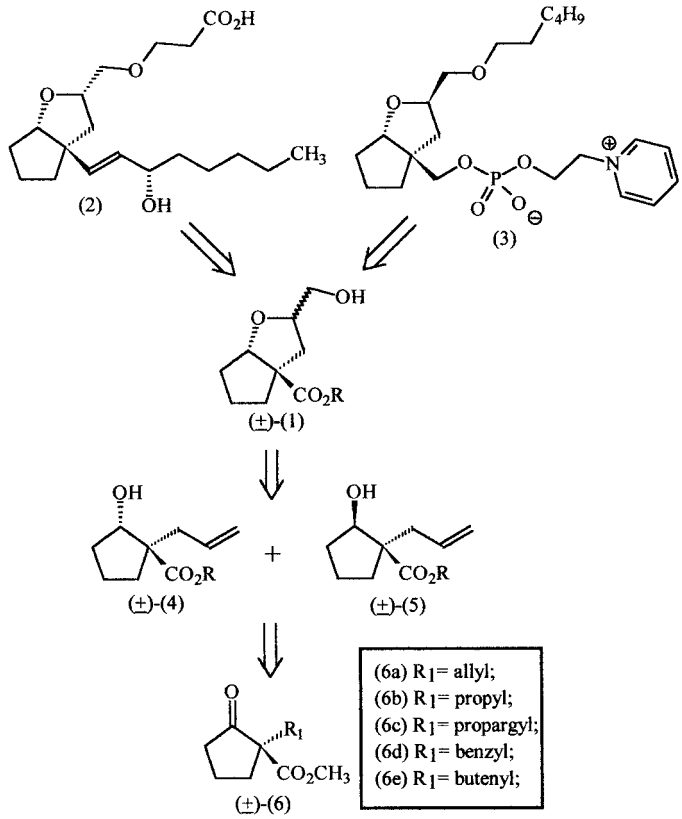
chelating agents were studied. This process is influenced more by steric than chelation factors, yielding the isomeric alcohols *syn* (13–23) and *anti* (14–24) in good diastereomeric excess.

2-Oxabicyclo[3.3.0]octane derivatives (1) constitute attractive synthons to new antithrombotic compounds, e.g., a prostacyclin (PGI_2) analogue[1] (2) and new PAF antagonists[2] (3) (Scheme 1).



Scheme 1.

Previous results described an efficient method to obtain, diastereoselectively, 2-allyl-2-alkoxycarbonyl-cyclopentanol derivatives (4) and (5)

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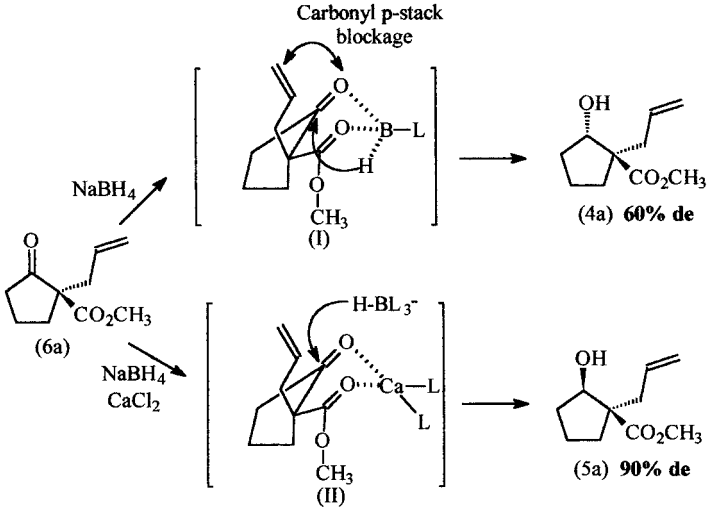
from cyclopentanone (6) employing sodium borohydride as the reducing agent, in the presence or absence of calcium chloride.[3] The cyclopentanol derivative (4) can be converted into the bicyclic compound (1) applying the diastereoselective cationic oxidative cyclization process.[4] The initial study showed that the diastereoselectivity of this process was sensitive to the bulk of the reducing species and to the size of the alkoxycarbonyl group present in these derivatives.[3] Moreover, by changing the alkyl group (R) from allyl (6a) to propyl (6b), propargyl (6c), benzyl (6d) and butenyl (6e), we showed that the reductive process with sodium borohydride is mainly dependent on steric factors. In the 2-allyl derivative (6a), the reduction is particularly influenced by carbonyl π-stack type blockage suggested by the mechanism illustrated in Scheme 2.[5,6]



Scheme 2.

In this paper, we describe the chemo and diastereoselective reduction of 2-acetyl-2-alkyl-γ-butyrolactones (7–12) designed as analogues of 2-alkyl-2-alkoxycarbonyl-cyclopentanone derivatives (6). The present study aims at identifying the effect of a conformationally free ketone group on the diastereoselectivity of the reductive process.

C-2 alkylated β-keto-esters (8–12) were prepared, in moderate yield (13 to 93%), from commercially available 2-acetyl-γ-butyrolactone[7] (7) using modified Barco's conditions[8,9] (Table 1).

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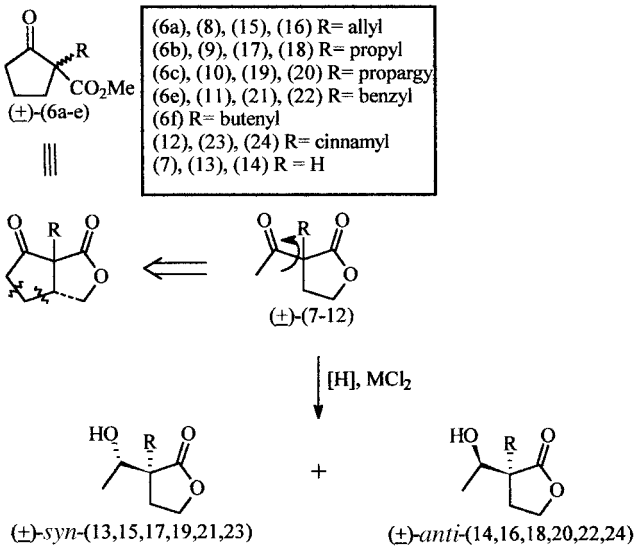
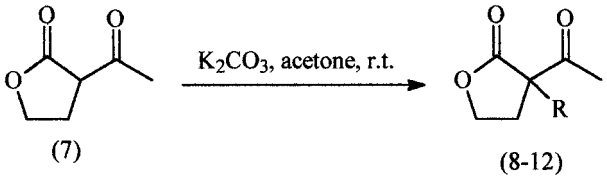


Scheme 3.

Table 1. Alkylation of the 2-Acetyl-γ-butyrolactone (7) with Alkyl Bromides



Entry	Product	Alkylant Agent	Reaction Time (h)	Yield (%)
1	(8) R=allyl	Allyl bromide	6	93
2	(9) R=propyl	Propyl bromide	48	13
3	(10) R=propargyl	Propargyl bromide	17	91
4	(11) R=benzyl	Benzyl bromide	6	63
5	(12) R=cinnamyl	Cinnamyl bromide	2	83

Compounds (7–12) were spectroscopically fully characterized and then submitted to several reduction conditions, to give the corresponding diastereomeric alcohols (13–24) in yields ranging from 53 to 96% (Table 2).

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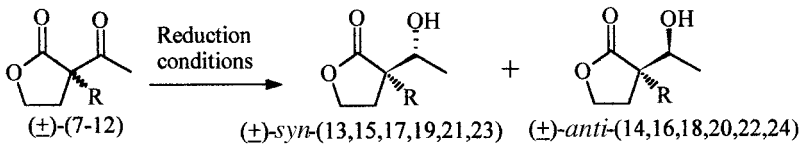
Table 2. Reduction of the 2-Acetyl-2-alkyl-γ-butyrolactone Derivatives (7–12)



Entry	Compound	Conditions[a]	Solvent	T (°C)	MCl_2	Product	Yield (%)	Rate[b,c] *syn* : *anti*
1	(7) R=H	A	MeOH	0°C	–	13–14	31	1 : 1.8
2	(7) R=H	A	MeOH	0°C	$CaCl_2$	13–14	44	1 : 8.4
3	(8) R=allyl	A	MeOH	r.t.	–	15–16	79	1 : 1
4	(8) R=allyl	A	MeOH	r.t.	$CaCl_2$	15–16	66	1 : 2
5	(8) R=allyl	A	MeOH	0°C	–	15–16	88	1.4 : 1
6	(8) R=allyl	A	MeOH	0°C	$CaCl_2$	15–16	96	1 : 1.9
7	(8) R=allyl	A	MeOH	−78°C	–	15–16	76	1 : 1
8	(8) R=allyl	A	MeOH	−78°C	$CaCl_2$	15–16	87	1 : 1.7
9	(8) R=allyl	A	MeOH	0°C	$MgCl_2$	15–16	60	1 : 1.2
10	(8) R=allyl	A	MeOH	0°C	$MnCl_2$	15–16	81	1 : 1.5
11	(8) R=allyl	A	MeOH	0°C	$CeCl_3$	15–16	79	1 : 2.2
12	(8) R=allyl	A	IprOH	0°C	–	15–16	77	1.2 : 1
13	(8) R=allyl	A	IprOH	0°C	$CaCl_2$	15–16	78	1.9 : 1
14	(8) R=allyl	B	THF	−78°C	–	15–16	68	1 : 7.6
15	(8) R=allyl	B	THF	−78°C	$CaCl_2$	15–16	80	1 : 5.7
16	(9) R=propyl	A	MeOH	0°C	–	17–18	94	1.4 : 1
17	(9) R=propyl	A	MeOH	0°C	$CaCl_2$	17–18	82	1 : 2
18	(10) R=propargyl	A	MeOH	0°C	–	19–20	62	1 : 1.4
19	(10) R=propargyl	A	MeOH	0°C	$CaCl_2$	19–20	53	1 : 2.4
20	(11) R=benzyl	A	MeOH	0°C	–	21–22	79	1 : 1
21	(11) R=benzyl	A	MeOH	0°C	$CaCl_2$	21–22	63	1 : 2.5
22	(12) R=cinnamyl	A	MeOH	0°C	–	23–24	99	1.8 : 1
23	(12) R=cinnamyl	A	MeOH	0°C	$CaCl_2$	23–24	96	1 : 2

[a]Conditions: A-$NaBH_4$ (1.2 eq.), solvent, MCl_2 (2 eq.), T°C, 30 min; B-L-Selectride (1.5 eq.), THF, MCl_2 (2 eq.), −78°C (30 min) → 0°C (15 min). [b]The relative diastereomeric ratio was determined by HRGC in a 10% de 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m × 0.3 mm × 0.3 μm) at

The composition of the diastereomeric alcohols mixture (13–24) was elucidated by NMR spectroscopy (nOe investigations included) (Table 3) and the relative diastereomeric ratio determined by HRGC (Table 2), using a β-cyclodextrin derivative as the stationary phase. The diastereomeric

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Table 3. Spectroscopic Data for 2-Alkyl-γ-butyrolactone Derivatives (7–24)

Compound	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$/TMS), δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ
7 (R=H)	1158 (ν C-O), 1720 (ν C=O), 1770 (ν C=O lactone).	2.31 [dddd, 1H, J = 6.3, 7.3, 7.6, 15.0, CH_2-4]; 2.45 [s, 3H, CH_3], 2.79 [ddt, 1H, J = 6.7; 8.0, 13.1, CH_2-4], 3.71 [dd, 1H, J = 6.7, 9.2, CH_2-5], 4.35 [dddd, 1H, J = 6.6, 7.9, 9.0, 16.8, CH_2-5].	23.4 (CH_2-4), 29.1 (CH_3), 52.6 (CH-3), 67.1 (CH_2-5), 172.5 (CO_2), 200.0 (C=O).
13–14 (R=H)	1025 (ν C-O alcool), 1179 (ν C-O), 1755 (ν C=O), 3414 (ν O-H).	1.26 [d, 6H, J = 6.3, CH_3], 2.02 [dddd, 2H, J = 6.6, 9.0, 10.5, 17.2, CH_2-4], 2.34 [dddd, 2H, J = 2.1, 6.3, 7.5, 13.8, CH_2-4], 2.55 [dt, 2H, J = 8.7, 11.4, CH-3], 3.93 [q, 1H, J = 6.3, CH(OH)], 3.97 [q, 1H, J = 6.3, CH(OH)], 4.24 [ddd, 2H, J = 6.6, 9.0, 10.6, CH_2-5], 4.41 [dt, 2H, J = 1.8, 9.0, CH_2-5].	20.4 (CH_3), 25.4 (CH_2-4), 45.4 (CH-3), 66.7 (CH_2-5), 67.9 [CH(OH)], 179.4 (CO_2).
8 (R=allyl)	1172 (ν C-O), 1642 (ν C=C), 1713 (ν C=O), 1767 (ν C=O lactone).	2.11 [dt, 1H, J = 9.0, 12.9, CH_2-4], 2.35 [s, 3H, CH_3], 2.64 [ddt, 1H, J = 1.2, 6.6, 14.4, CH_2-CH=CH_2], 2.78 [ddt, 1H, J = 1.2, 7.8, 14.2, CH_2-CH=CH_2], 2.88 [ddd, 1H, J = 3.3, 7.5, 13.0, CH_2-4], 4.19 [dt, 1H, J = 7.2, 9.0, CH_2-5], 4.30 [dt, 1H, J = 3.3, 9.0, CH_2-5], 5.19 [m, 2H, CH_2-CH=CH_2], 5.60 [m, 1H, CH_2-CH=CH_2].	25.5 (CH_3), 28.5 (CH_2-4), 38.7 (CH_2-CH=CH_2), 60.7 (C-3), 66.1 (CH_2-5), 120.0 (CH_2-CH=CH_2), 131.1 (CH_2-CH=CH_2), 174.9 (CO_2), 201.9 (C=O).

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15–16 (R=allyl)	1193 (ν C-O), 1641 (ν C=C), 1747 (ν C=O), 3446 (ν O-H).	1.21 [d, 3H, $J=6.6$, CH_3 *syn*], 2.4 [d, 3H, $J=6.6$, CH_3 *anti*], 2.01 [ddd, 1H, $J=4.8$, 8.1, 12.9, CH_2-4 *syn*], 2.16 [ddd, 1H, $J=4.8$, 8.1, 13.2, CH_2-4 *anti*], 2.3 [m, 4H, $CH_2CH{=}CH_2$], 2.46 [ddd, 1H, $J=$ 7.8, 9.3, 12.9, CH_2-4 *syn*], 2.63 [ddt, 1H, $J=1.2$, 6.3, 13.8, CH_2-4 *anti*], 3.94 [q, 1H, $J=6.0$, C*H*(OH) *anti*], 4.06 [q, 1H, $J=6.6$, C*H*(OH) *syn*], 4.20 [m, 2H, CH_2-5], 4.29 [dddd, 2H, $J=1.2$, 4.5, 9.0, 13.0, CH_2-5], 5.20 [m, 4H, $CH_2CH{=}CH_2$], 5.77 [m, 2H, $CH_2CH{=}CH_2$].	17.5 (CH_3 *anti*), 17.7 (CH_3 *syn*), 26.1 (CH_2-4 *syn*), 29.2 (CH_2-4 *anti*), 36.9 ($CH_2CH{=}CH_2$ *anti*) 38.7 ($CH_2CH{=}CH_2$ *syn*), 50.6 (C-3 *anti*), 52.6 (C-3 *syn*), 6.1 (CH_2-5 *syn*), 66.1 (CH_2-5 *anti*), 69.7 [*C*H(OH) *syn*], 71.3 [*C*H(OH) *anti*], 119.5 ($CH_2CH{=}CH_2$ *syn*), 119.6 ($CH_2CH{=}CH_2$ *anti*), 132.1 ($CH_2CH{=}CH_2$ *syn*), 132.5 ($CH_2CH{=}CH_2$ *anti*), 180.7 (C=O *syn*), 180.8 (C=O *anti*).
15 (R=allyl)	1217 and 1253 (ν C-O), 1549 (ν C=C), 1775 (ν C=O), 3516 (ν O-H).	1.21 [d, 3H, $J=6.6$, CH_3], 2.01 [ddd, 1H, $J=4.8$, 8.4, 12.8, CH_2-4], 2.23 [dd, 1H, $J=8.1$, 13.6, $CH_2CH{=}CH_2$], 2.37 [ddt, 1H, $J=$ 1.2, 6.9, 13.5, $CH_2CH{=}CH_2$], 2.46 [ddd, 1H, $J=7.8$, 9.3, 12.9, CH_2-4], 4.06 [q, 1H, $J=6.6$, C*H*(OH)], 4.21 [q, 1H, $J=8.4$, CH_2-5], 4.28 [ddd, 1H, $J=4.5$, 9.0, 13.5, CH_2-5], 5.18 [m, 2H, $CH_2CH{=}CH_2$], 5.77 [dddd, 1H, $J=6.9$, 8.1, 9.5, 17.0, $CH_2CH{=}CH_2$].	17.7 (CH_3), 26.1 (CH_2-4), 38.7 ($CH_2CH{=}CH_2$), 52.6 (C-3), 6.1 (CH_2-5), 69.7 [*C*H(OH)], 119.5 ($CH_2CH{=}CH_2$), 132.1 ($CH_2CH{=}CH_2$), 180.7 (C=O).

(*continued*)

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Table 3. Continued

Compound	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$/TMS), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ
16 (R=allyl)	1191 (ν C-O), 1549 (ν C=C), 1765 (ν C=O), 3509 (ν O-H).	1.24 [d, 3H, $J=6.3$, CH_3], 2.16 [ddd, 1H, $J=4.8$, 8.1, 13.2, CH_2-4], 2.28 [m, 2H, $CH_2CH=CH_2$], 2.63 [ddt, 1H, $J=1.2$, 6.3, 13.8, CH_2-4], 3.94 [q, 1H, $J=6.0$, CH(OH)], 4.21 [q, 1H, $J=9.0$, CH_2-5], 4.29 [ddd, 1H, $J=4.8$, 9.3, 13.0, CH_2-5], 5.21 [m, 2H, $CH_2CH=CH_2$], 5.78 [dddd, 1H, $J=6.3$, 9.0, 9.3, 17.5, $CH_2CH=CH_2$].	17.5 (CH_3), 29.2 (CH_2-4), 36.9 ($CH_2CH=CH_2$), 50.6 (C-3), 66.15 (CH_2-5), 71.3 [CH(OH)], 119.6 ($CH_2CH=CH_2$), 132.5 ($CH_2CH=CH_2$), 180.8 (C=O).
9 (R=propyl)	1171 (ν C-O), 1713 (ν C=O), 1763 (ν C=O lactone).	0.96 [t, 3H, $J=7.2$, $-CH_2CH_2CH_3$], 1.23 [m, 2H, $-CH_2CH_2CH_3$], 1.76 [ddd, 1H, $J=5.4$, 10.2, 15.6, $CH_2CH_2CH_3$], 2.02 [dt, 1H, $J=9.0$, 12.9, CH_2-4), 2.11 [ddd, 1H, $J=5.4$, 10.2, 15.6, $-CH_2CH_2CH_3$], 2.32 [s, 3H, (C=O)CH_3], 2.93 [ddd, 1H, $J=3.0$, 7.2, 10.8, CH_2-4], 4.14 [dt, 1H, $J=6.9$, 9.3, CH_2-5], 4.28 [dt, 1H, $J=3.3$, 8.7, CH_2-5].	13.9 ($CH_2CH_2CH_3$), 18.1 ($CH_2CH_2CH_3$), 25.2 [(C=O)CH_3], 28.8 (CH_2-4), 36.9 ($CH_2CH_2CH_3$), 61.4 (C-3), 66.0 (CH_2-5), 175.4 (CO_2), 202.3 (C=O).
17–18 (R=propyl)	1197 (ν C-O), 1747 (ν C=O), 3455 (ν C-OH).	0.93 [t, 3H, $J=6.9$, $CH_2CH_2CH_3$ *syn*], 0.96 [t, 3H, $J=7.2$, $CH_2CH_2CH_3$ *anti*], 1.18 [d, 3H, $J=6.6$ (C=O) CH_3 *syn*], 1.23 [d, 3H, $J=6.3$, (C=O) CH_3 *anti*], 1.41 [m, 4H,	14.2 ($CH_2CH_2CH_3$, *syn*) and 14.3 ($CH_2CH_2CH_3$, *anti*), 17.4 ($CH_2CH_2CH_3$, *syn* and *anti*), 17.5 [(C=O)CH_3, *syn*], 17.7 [(C=O)CH_3, *anti*], 26.5

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		$CH_2CH_2CH_2CH_3$], 1.61 [dd, 1H, $J=5.1$, 12.6, $CH_2CH_2CH_2CH_3$ *syn*], 180 [td, 1H, $J=4.5$, 13.0, $CH_2CH_2CH_2CH_3$ *anti*], 1.94 [ddd, 1H, $J=4.2$, 8.1, 12.9, CH_2-4 *syn*], 2.12 [ddd, 1H, $J=4.5$, 8.4, 13.2, CH_2-4 *anti*], 2.27 [ddd, 1H, $J=7.8$, 9.3, 13.0, CH_2-4 *anti*], 2.51 [ddd, 1H, $J=8.1$, 9.6, 12.9, CH_2-4], 3.92 [q, 1H, $J=6.0$, C*H*(OH) *anti*], 4.08 [q, 1H, $J=6.3$, C*H*(OH) *syn*], 4.23 [q, 2H, $J=8.1$, CH_2-5, *syn* and *anti*], 4.32 [td, 2H, $J=2.7$, 5.4, 9.0, 9.1, CH_2-5, *syn* and *anti*].	($CH_2CH_2CH_2CH_3$, *syn*), 29.8 ($CH_2CH_2CH_2CH_3$, *anti*), 34.8 (CH_2-4, *syn*), 36.7 (CH_2-4, *anti*), 50.6 (C-3, *syn*), 52.7 (C-3, *anti*), 66.0 (CH_2-5, *syn*), 66.1 (CH_2-5, *anti*), 180.2 (CO_2, *syn*), 180.3 (CO_2, *anti*).
10 (R=propargyl)	1167 (ν C-O), 1713 (ν C=O), 1755 (ν C=O lactone), 2118 (ν C≡C), 3251 (ν C≡C-H).	2.09 [t, 1H, $J=2.7$, C≡C-*H*], 2.33 [dt, 1H, $J=9.0$, 13.2, CH_2-4], 2.36 [s, 3H, (C=O)CH_3], 2.74 [dd, 1H, $J=2.4$, 17.1, -CH_2C≡C-H], 2.95 [ddd, 1H, $J=3.3$, 7.5, 13.3, CH_2-4], 2.97 [dd, 1H, $J=2.7$, 17.1, -CH_2C≡C-H], 4.28 [dt, 1H, $J=7.2$, 9.0, CH_2-5], 4.39 [dt, 1H, $J=3.3$, 9.0, CH_2-5].	24.4 ($CH_2C{\equiv}CH_3$), 25.4 [(C=O)CH_3], 29.3 (CH_2-4), 60.0 (C-3), 66.4 (CH_2-5), 72.0 (-C≡*C*-H), 77.7 (-*C*≡C-H), 173.9 (CO_2), 200.5 (C=O).
19–20 (R=propargyl)	1191 (ν C-O), 1751 (ν C=O), 2119 (ν C≡C), 3289 (ν C≡C-H), 3440 (ν C-OH).	1.23 [d, 3H, $J=6.6$, -CH(OH)CH_3, *syn*], 1.24 [d, 3H, $J=6.6$, -CH-(OH)CH_3, *anti*], 2.06 [t, 1H, $J=2.7$, C≡C-*H*, *syn*], 2.07 [t, 1H, $J=2.7$, C≡C-*H*, *anti*], 2.43 [dd, 1H,	17.6 [(C=O)CH_3, *syn* and *anti*], 22.0 ($CH_2C{\equiv}CH_3$, *syn*), 22.4 ($CH_2C{=}CH_3$, *anti*), 26.9 and 29.6 (CH_2-4, *syn* and *anti*), 50.5 and 52.1 (C-3, *syn*

(*continued*)

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Table 3. Continued

Compound	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$/TMS), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ
		J = 2.7, 17.1, $CH_2C{\equiv}C$-H, *syn*], 2.43 [m, 4H, CH_2-4, *syn* and *anti*], 2.55 [dd, 1H, *J* = 3.0, 16.7, $CH_2C{\equiv}C$-H, *anti*], 2.57 [dd, 1H, *J* = 2.4, 16.8, $CH_2C{\equiv}C$-H, *anti*], 2.69 [dd, 1H, *J* = 2.7, 16.8, $CH_2C{\equiv}C$-H, *syn*], 3.99 [q, 1H, *J* = 6.3, $CH(OH)CH_3$, *anti*], 4.05 [q, 1H, *J* = 6.3, $CH(OH)CH_3$, *syn*], 4.37 [m, 4H, CH_2-5, *syn* and *anti*].	and *anti*), 66.3 and 66.5 (CH_2-5, *syn* and *anti*), 69.7 [*C*H(OH) CH_3, *anti*], 70.9 [*C*H(OH)CH_3 *syn*], 71.1 (-C≡C-H, *syn* and *anti*), 79.0 and 79.4 (CH_2-5, *syn* and *anti*).
11 (R=benzyl)	1178 (ν C-O), 1696 (ν C=O), 1770 (ν C=O).	2.11 [ddd, 1H, *J* = 8.1, 8.4, 13.2, CH_2-4], 2.41 [s, 3H, (C = O)CH_3], 2.78 [ddd, 1H, *J* = 4.5, 7.7, 13.1, CH_2-4], 3.11 [d, 1H, *J* = 14.1, $CH_2C_6H_5$], 3.42 [d, 1H, *J* = 13.8, $CH_2C_6H_5$], 3.77 [dt, 1H, *J* = 4.2, 8.7, CH_2-5], 4.05 [dt, 1H, *J* = 8.1, 8.7, CH_2-5], 7.15 [dd, 2H, *J* = 2.4, 7.8, $CH_2C_6H_5$], 7.28 [m, 3H, $CH_2C_6H_5$].	25.7 [(C=O)CH_3], 28.1 (CH_2-4), 39.6 ($CH_2C_6H_5$), 62.2 (C-3), 127.3, 128.6, 129.4 and 134.9 ($CH_2C_6H_5$) 175.4 (CO_2), 202.0 [(*C*=O)CH_3].

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21–22 (R=benzyl)	1181 (ν C-O), 1747 (ν C=O), 3483 (ν O-H).	1.29 [d, 6H, $J=6.3$, CH(OH)CH_3], 2.04 [ddd, 1H, $J=3.3$, 8.4, 13.0, CH_2-4, *syn*], 2.17 [m, 1H, CH_2-4, *anti*], 2.44 [dt, 1H, $J=9.0$, 12.9, CH_2-4, *syn*], 2.67 [d, 1H, $J=13.2$, C$H_2C_6H_5$, *syn*], 2.80 [d, 1H, $J=13.2$, C$H_2C_6H_5$, *anti*], 3.02 [d, 1H, $J=12.9$, C$H_2C_6H_5$, *syn*], 3.11 [q, 1H, $J=8.7$, C*H*(OH)CH_3, *anti*], 3.28 [d, 1H, $J=13.5$, C$H_2C_6H_5$, *anti*], 4.02 [m, 4H, CH_2-5], 7.26 [m, 10H, $CH_2C_6H_5$].	17.3 and 17.9 [CH(OH)*C*H_3] 25.6 and 28.8 (CH_2-4), 37.4 and 39.9 (*C*$H_2C_6H_5$), 52.2 and 54.6 (C-3), 65.8 and 65.9 (CH_2-5), 70.0 and 71.7 [*C*H(OH)CH_3], 127.0, 128.5, 129.6 and 136.1 (C$H_2C_6H_5$), 181.0 and 181.6 (CO_2).
12 (R=cinnamyl)	701 and 750 (δ = C-H), 1171 (ν C-O), 1709 (ν C=O), 1763 (ν C=O lactone).	2.19 [dt, 1H, $J=9.0$, 12.9, CH_2-4], 2.39 [s, 3H, (C=O)CH_3], 2.86 [dt, 2H, $J=2.4$, 6.0, CH_2-4], 2.89 [ddd, 1H, $J=3.3$, 7.2, 13.2, CH_2CH=CHC_6H_5], 4.19 [dt, 1H, $J=7.5$, 8.7, CH_2-5], 4.29 [dt, 1H, $J=3.6$, 9.3, CH_2-5], 5.97 [ddd, 1H, $J=6.6$, 8.1, 15.9, CH_2C*H*=CHC_6H_5], 6.52 (dt, 1H, $J=1.2$, 15.9, CH_2CH=C*H*C_6H_5), 7.3 (m, 5H, CH_2CH=CHC$_6H_5$].	25.1 [(C=O)*C*H_3], 29.5 (CH_2-4), 38.3 (CH_2*C*H=CHC_6H_5), 126.7, 128.1, 128.8 (CH_2CH=CH*C*$_6H_5$), 135.4 (CH_2CH=*C*HC$_6H_5$), 136.6 (CH_2CH=CH-*C*$_6H_5$), 176.7 (CO_2), 202.8 [(C=O)CH_3].

(*continued*)

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Table 3. Continued

Compound	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$/TMS), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ
23–24 (R=cinnamyl)	1173 (ν C-O), 1770 (ν C=O lactone), 3470 (ν O-4).	1.24 (d, 3H, $J=6.3$, $CH(OH)CH_3$, *syn*), 1.27 (d, 3H, $J=6.6$, $CH(OH)CH_3$, *anti*), 2.04 (ddd, 1H, $J=4.2$, 8.4, 14.4, CH_2-4, *anti*), 2.20 (ddd, 1H, $J=4.8$, 8.4, 18.3, CH_2-4, *syn*), 2.4 (m, 5H, CH_2-4 and $CH_2CH=CHC_6H_5$), 2.79 (ddd, 1H, $J=1.5$, 6.3, 13.8, CH_2-4, *anti*), 3.99 (q, 1H, $J=6.3$, $CH(OH)CH_3$, *anti*), 4.11 (q, 1H, $J=6.3$, $CH(OH)CH_3$, *syn*), 4.24 (m, 4H, CH_2-5), 6.13 (ddd, 2H, $J=6.6$, 9.0, 15.6, $CH_2CH=CHC_6H_5$), 6.53 (dd, 2H, $J=10.9$, 11.1, $CH_2CH=CHC_6H_5$), 7.28 (m, 10H, $CH_2CH=CHC_6H_5$).	17.6 [$CH(OH)CH_3$, *anti*, 17.8 ($CH(OH)CH_3$, *syn*), 26.4 (CH_2-4, *syn*), 29.5 (CH_2-4, *anti*), 35.8 ($CH_2CH=CHC_6H_5$, *anti*), 37.9 ($CH_2CH=CHC_6H_5$, *syn*), 50.9 (C-3, *anti*), 52.9 (C-3, *syn*), 62.2 (CH_2-5, *syn* and *anti*), 69.8 [$CH(OH)CH_3$, *syn*), 71.3 [$CH(OH)CH_3$, *anti*), 123.3 ($CH_2CH=CHC_6H_5$, *syn*), 123.7 ($CH_2CH=CHC_6H_5$, *anti*), 126.1, 127.1 and 128.5 (CH_2 $CH=CHC_6H_5$, *syn* and *anti*), 134.4 ($CH_2CH=CHC_6H_5$, *anti*), 136.5 ($CH_2CH=CHC_6H_5$, *syn*), 168.6 and 180.7 (CO_2, *syn* and *anti*).

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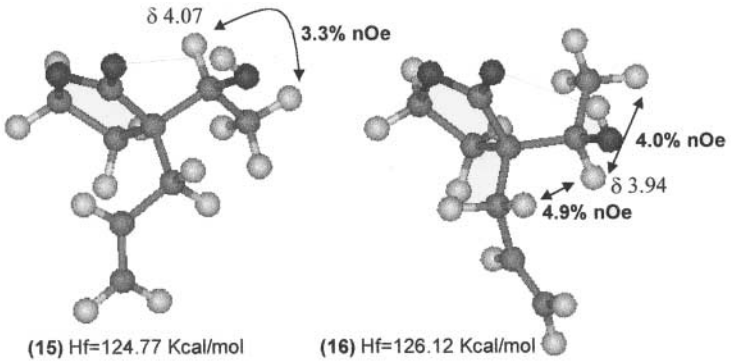
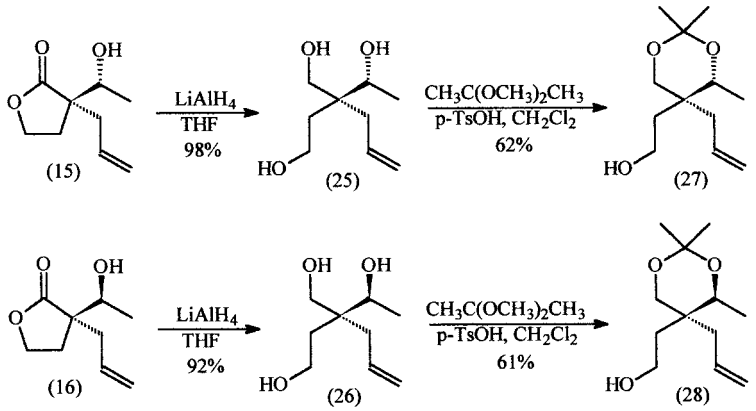
mixture of the allyl-alcohols (15) and (16) was separated by silica gel column chromatography. Their relative configurations were assigned by nOe-experiments, which showed a positive correlation (4.9%) between the carbinolic hydrogen and the methylenic hydrogen atom of the allyl substituent in the compound (16) (Scheme 4). Considering that pseudo-rotation of five



Scheme 4.

membered rings can influence the results from nOe experiments, we decided to correlate them with minimal energy conformers of (15) and (16). Then, molecular modeling studies of the derivatives (15) and (16) were carried out using the AM1 Hamiltonian.[10] After geometry optimizations, we are able to find the minimal energy conformation of (15) and (16), which presented a heat formation of 124.77 and 126.12 Kcal/mol, respectively (Scheme 4). The relative configuration was confirmed by derivation, through the formation of less conformationally flexible six-membered ring ketal derivatives (27) and (28), which were characterized by NMR spectroscopy, as described in the previous work by Takeshita et al.[11] (Scheme 5). These results were extended for all structurally correlated derivatives, since they presented the same spectroscopic pattern, as presented in Table 3.

There are striking aspects of the data displayed in Table 2. Firstly, in comparison with the profile of the correspondent cyclopentanone derivatives, e.g. (6a) (Scheme 2), the increase of the conformational freedom of the ketone carbonyl group in butyrolactone derivative (8), resulted in a decrease of the diastereoselectivity of the reductive process with sodium borohydride in the absence or in the presence of calcium chloride (Entries 3 and 4). Nevertheless, most studies showed that the reduction of compounds

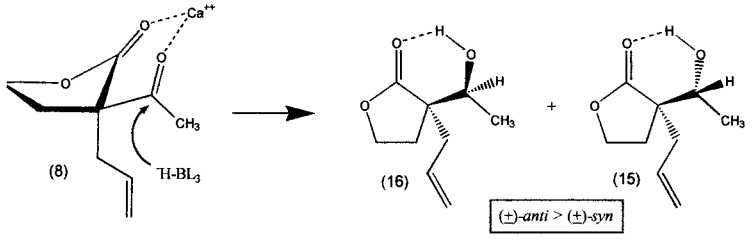


Scheme 5.

(8–13) leads to preferential formation of the alcohol presenting the *anti* configuration (Table 2).

The reduction of allyl derivative (8), under a variety of conditions (Table 2), which include changing the reaction temperature from r.t. (Entries 3 and 4) to 0°C (Entries 5 and 6) and −78°C (Entries 7 and 8), did not significantly increase the diastereoselectivity.

The use of $CaCl_2$ as complexating agent in reductions mediated by sodium borohydride (Entries 1 *vs* 2, 3 *vs* 4, 5 *vs* 6, 7 *vs* 8) increased the diastereoselectivity of the process, possibly due to the fixation of a pseudo-periplanar conformation (Scheme 6), which favored the hydride attack from the opposite carbonyl face. On the other hand, other Lewis acids selected according to previously reported procedures,[12,13] i.e. $MgCl_2$ (Entry 9), $MnCl_2$ (Entry 10) and $CeCl_3$ (Entry 11), did not lead to remarkable variations on the diastereoselectivity.



Scheme 6.

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Interestingly, the change of the solvent from methanol to isopropanol (entries 6 *vs* 13) led to an inversion of the diastereoselectively, with the formation of the *syn* alcohol (15) in 34% diastereomeric excess. This distinct profile may be explained by the presence of different reducing species in the media, since sodium borohydride reacts with methanol to give sterically demanding trimethoxyborohydride [$(MeO)_3BH^-$], whereas solutions of sodium borohydride in isopropanol are very stable.[14]

Reducing the allyl-substituted derivative (8) using bulky lithium tri-sec-butyl-borohydride (L-Selectride)[15] led to the formation of the alcohol presenting *anti* configuration (16) in a greater diastereomeric excess (77%) (entry 14). Curiously, the use of $CaCl_2$ in the reductive process mediated by L-Selectride (Entry 15) decreased the diastereoselectivity, probably due to exchanging the counter-ion reducing agent from monovalent lithium to divalent calcium ion, resulting in the formation of a more bulky dimeric form of Selectride.

Varying the C-2 substituent from propyl (9) (Entries 16 and 17), to propargyl (10) (Entries 18 and 19), benzyl (11) (Entries 20 and 21) and cinnamyl (12) (Entries 22 and 23), allowed us to conclude that the electronic variations of these substituents did not affect substantially the diastereoselectivity of the reductive process. Benzyl (11) (Entries 20 and 21) and cinnamyl derivatives (12) (Entries 22 and 23) presented a slightly higher diastereoselectivity profile, probably because of steric effects.

In conclusion, the results obtained from this research work indicated that, contrary to the diastereoselective reductive behavior previously described for the 2-allyl-2-carbomethoxy-cyclopentanone derivative (6a), the diastereoselectivity of 2-acetyl-2-alkyl-γ-butyrolactones (8–12) reduction using borohydrides is more dependent on steric interactions than on chelation factors.

The substituted γ-butyrolactone derivatives disclosed in this work are useful for the synthesis of natural chiral compounds[16] and constitute an attractive synthon to new bioactive compounds, e.g., anticonvulsants[17,18] and antitumoral[19] agents, muscarinic antagonists[20] and conformationally semirigid diacylglycerol analogues.[21,22]

EXPERIMENTAL

^{1}H-NMR spectra were determined in deuterated chloroform, containing *ca*. 0.3% tetramethylsilane as an internal standard, with UNITY plus-300 at 300 MHz, Brucker AC 200 or Varian VRX 200 at 200 MHz. Splitting patterns are as follows: br, broad; s, singlet; d, doublet; dd, double

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doublet; ddd, double double doublet, dddd, double double double doublet; td, triple doublet; t, triplet; dt, double triplet; ddt, double double triplet; q, quartet; m, multiplet. ^{13}C-NMR spectra were determined in the same spectrometers described above at 75 or 50 MHz, employing the same solvents. Infrared (IR) spectra were obtained with Nicolet 505 Magna spectrophotometers by using sodium chloride cell or potassium bromide plates. Gas chromatography (HRGC) were recorded in a Hewlett Packard model 5890 series II using injection in the split mode. The HRGC analysis were performed in 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 (1% vinyl; 5% phenyl; 94% methylpolysiloxane) house made capillary column (20 m × 0.3 mm × 0.3 μm) at 100°C/2°C/min to 130°C. Microanalysis data was obtained with Perkin Elmer 240 analyzer, using Perkin Elmer AD-4 balance.

The progress of all reactions was monitored by tlc, which was performed on aluminum sheets precoated with silica gel 60 (HF-254, Merck) of 0.25 mm thickness. The eluents used for tlc were: Mixture A: AcOEt : hexane (3 : 7), and Mixture B: isopropanol : hexane (1 : 9). The developed chromatograms were viewed under ultraviolet light or iodine revelation. For column chromatography Merck silica-gel (70–230 mesh) was used. Solvents used in the reactions were redistilled prior to use and stored over 3–4 Å molecular sieves. Reactions were generally carried out under nitrogen atmosphere and magnetic stirring. The usual work-up means that the organic extracts prior to concentration under reduced pressure, were treated with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and filtered.

General Procedure for the C-Alkylation of the 2-Acetyl-γ-butyrolactone (7)

To a suspension of anhydrous potassium carbonate (3.23 g; 23.4 mmol) in acetone (8 mL) was added 2-acetyl-γ-butyrolactone (1 g; 7.8 mmol). The reaction mixture displays a characteristic yellow color after stirring at room temperature for 30 min. Then, the respective alkyl bromide (9.4 mmol) was added slowly and the mixture was stirred at room temperature for 2–48 h (monitored by tlc, mixture A as eluent). The suspension formed was filtered, the organic solution concentrated at reduced pressure (80 mmHg) and the residue diluted with ether (40 mL). The ''usual work-up'' gave the respective 2-acetyl-2-alkyl-γ-butyrolactone (8–12).

2-Acetyl-2-allyl-γ-butyrolactone (8): This compound was obtained in 93% yield as a colorless oil, from alkylation of (7) with allyl bromide (1.12 g;

0.8 mL), after 6 h (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.09.

2-Acetyl-2-propyl-γ-butyrolactone (9): This compound was obtained in 13% yield as a colorless oil, from alkylation of (7) with propyl bromide (1.16 g; 0.9 mL), after 48 h (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.62; H, 8.20.

2-Acetyl-2-propargyl-γ-butyrolactone (10): This compound was obtained in 91% yield as a colorless oil, from alkylation of (7) with propargyl bromide (1.11 g; 0.7 mL), after 17 h (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.94; H, 6.13.

2-Acetyl-2-benzyl-γ-butyrolactone (11): This compound was obtained in 63% yield as a white solid (m.p. 56–58°C), from alkylation of (7) with benzyl bromide (1.6 g; 1.1 mL), after 6 h (for spectroscopic data see Table 3). Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.59.

2-Acetyl-2-cinnamyl-γ-butyrolactone (12): This compound was obtained in 83% yield as a light yellow solid (m.p. 67–68°C), from alkylation of (7) with cinnamyl bromide (1.85 g; 1.4 mL), after 2 h (for spectroscopic data see Table 3). Anal. Calcd. for $C_{15}H_{16}O_3$: C, 71.75; H, 6.60. Found: C, 73.71; H, 6.53.

General Procedure for Reduction of 2-Acetyl-2-alkyl-γ-butyrolactone (7–12) with Sodium Borohydride, in the Presence or in the Absence of $CaCl_2$ (Reduction Condition A)

A solution of the 2-acetyl-2-alkyl-γ-butyrolactone derivative (7–12) (0.89 mmol) in solvent (methanol or isopropanol) (6 mL), in the presence or absence of the anhydrous calcium chloride (1.78 mmol), was stirred at room temperature for 30 min. The reaction mixture was cooled at 0°C (r.t. or −78°C), and 0.04 g (1.07 mmol) of sodium borohydride was slowly added. A clear solution was obtained, which was stirred for 30 min. The solvent was concentrated at reduced pressure (80 mmHg). The white doughy residue was diluted with methylene chloride (30 mL). The resulting solution was washed with saturated aqueous ammonium chloride solution (30 mL). Usual work-up of the organic layer afforded the mixture of diastereomeric alcohols as described in Table 2. The diastereomeric allyl alcohols mixture (15–16) was separated by silica gel (70–230 mesh) column chromatography using a mixture of hexane and isopropanol (99 : 1 to 90 : 10 v/v) as eluent (for spectroscopic data see Table 3).

(±)-2-[1′-(1′-Hydroxyethyl)]-γ-butyrolactone (13–14): This compound was obtained in 93% yield as a colorless oil (for spectroscopic data see

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Table 3). Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.48; H, 7.88.

(±)-2-Allyl-2-[1′-(1′-hydroxyethyl)]-γ-butyrolactone (15–16): This compound was obtained in 93% yield as a colorless oil (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.62; H, 8.44.

(±)-2-Propyl-2-[1′-(1′-hydroxyethyl)]-γ-butyrolactone (17–18): This compound was obtained in 13% yield as a colorless oil (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.63; H, 9.51.

(±)-2-Propargyl-2-[1′-(1′-hydroxyethyl)]-γ-butyrolactone (19–20): This compound was obtained in 91% yield as a colorless oil (for spectroscopic data see Table 3). Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.15; H, 7.11.

(±)-2-Benzyl-2-[1′-(1′-hydroxyethyl)]-γ-butyrolactone (21–22): This compound was obtained in 63% yield as a yellow oil (for spectroscopic data see Table 3). Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.04; H, 7.19.

(±)-2-Cinnamyl-2-[1′-(1′-hydroxyethyl)]-γ-butyrolactone (23–24): This compound was obtained in 83% yield as a light yellow oil (for spectroscopic data see Table 3). Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73,15; H, 7.37. Found: C, 73.28; H, 7.43.

Reduction of 2-Acetyl-2-allyl-γ-butyrolactone (8) with Lithium-tri-sec-butyl-borohydride, in the Presence or in the Absence of $CaCl_2$ (Reduction Condition B)

A solution of anhydrous 2-acetyl-2-allyl-γ-butyrolactone derivative (**8**) (0.89 mmol) in anhydrous THF (2 mL), under nitrogen atmosphere, in the presence or absence of the solution of calcium chloride in anhydrous THF (1 mL), was stirred at room temperature for 30 min. The reaction mixture was cooled at 78°C and 1.3 mL (1.3 mmoles) of 1 M solution of lithium-tri-sec-butyl-borohydride (L-Selectride) in anhydrous THF was added to it. The reaction mixture was stirred for 30 min, at −78°C, then for 15 min at 0°C, and afterwards 5 mL of 1 M solution of H_2O_2 and 7 mL of 0.2 N aqueous solution of NaOH were added. After 15 min, the system was diluted with ether (5 mL) and the organic layer was separated, washed with a saturated aqueous solution of sodium bisulfite (5 mL), and submitted to the ''usual work-up'' affording the mixture of diastereomeric alcohols as described in Table 2 (Entries 14 and 15).

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Reduction of (*syn*)-2-Allyl-2-[1′-(1′-hydroxy-ethyl)]-γ-butyrolactone (15) with Lithium Aluminumhydride

To a solution of lithium-aluminum-hydride (0.98 g, 25.8 mmol) in anhydrous THF (20 mL), under nitrogen atmosphere, was added at r.t. a solution of the *syn*-2-acetyl-2-allyl-γ-butyrolactone derivative (15) (0.44 g, 2.58 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred for 2 h, at r.t., and 20 mL of 1 M aq. solution of H_2O_2 and 28 mL of 0.2 N aq. solution of NaOH were added. After 15 min, the system was diluted with ethyl acetate (60 mL) and the organic layer was filtered off over celite column. The organic filtrate was evaporated under reduced pressure to afford (25) in 98% yield, as a colorless oil; ^{1}H NMR (300 MHz): 1.18 (d, 3H, $J = 6.6$ Hz, -CH(OH)CH_3), 1.51 (dt, 1H, $J = 4.6$ and 15.8 Hz, -CH_2CH$_2$OH), 2.02 (m, 3H, -CH_2CH$_2$OH and -CH_2CH=CH$_2$), 3.72 (q, 2H, $J = 11.5$ Hz, -CH_2OH), 3.82 (m, 2H, -CH$_2$CH_2OH), 3.94 (q, 1H, $J = 6.3$ Hz, -CH(OH)CH$_3$), 5.08 (m, 2H, -CH$_2$CH=CH_2), 5.78 (m, 1H, -CH$_2$CH=CH$_2$); ^{13}C NMR (75 MHz): 17.2 (-CH(OH)CH_3), 33.2 (-CH_2CH=CH$_2$), 38.8 (-CH_2CH$_2$OH), 43.2 (C-2), 58.4 (-CH$_2$CH_2OH), 68.2 (-CH_2OH), 72.9 (-CH(OH)CH$_3$), 118.0 (-CH$_2$CH=CH_2), 133.5 (-CH$_2$CH=CH$_2$). Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.93; H, 10.49.

Reduction of (*anti*)-2-Allyl-2-[1′-(1′-hydroxy-ethyl)]-γ-butyrolactone (16) with Lithium Aluminumhydride

To a solution of lithium-aluminum-hydride (0.45 g, 11.7 mmol) in anhydrous THF (10 mL), under nitrogen atmosphere, was added at r.t. a solution of the *anti*-2-acetyl-2-allyl-γ-butyrolactone derivative (16) (0.2 g, 1.17 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred for 2 h, at r.t., and afterwards 10 mL of 1 M aq. solution of H_2O_2 and 14 mL of 0.2 N aq. solution of NaOH were added. After 15 min, the system was diluted with ethyl acetate (30 mL) and the organic layer was filtered off celite in a sintered glass filter. The organic filtrate was evaporated under reduced pressure to afford (26) in 92% yield, as a colorless oil; ^{1}H NMR (300 MHz): 1.24 (d, 3H, $J = 6.4$ Hz, -CH(OH)CH_3), 1.94 (m, 4H, -CH_2CH$_2$OH and -CH_2CH=CH$_2$), 3.59 (d, 1H, $J = 11.3$ Hz, -CH_2OH), 3.81 (m, 3H, -CH_2OH and -CH$_2$CH_2OH), 4.11 (q, 1H, $J = 7.1$ Hz, -CH(OH)CH$_3$), 5.08 (m, 2H, -CH$_2$CH=CH_2), 5.77 (m, 1H, -CH$_2$CH=CH$_2$); ^{13}C NMR (75 MHz): 17.3 (-CH(OH)CH_3), 34.5 (-CH$_2$CH=CH$_2$), 36.6 (-CH_2CH$_2$OH), 43.4 (C-2), 58.1 (-CH$_2$CH_2OH), 66.5 (-CH_2OH), 71.6 (-CH(OH)CH$_3$), 118.1

(-$CH_2CH{=}CH_2$), 133.6 (-$CH_2CH{=}CH_2$). Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.12; H, 10.33.

Ketalization of (*syn*)-2-Allyl-2-[1′-(1′-hydroxy-ethyl)]-1,4-butanediol (25) with 2,2-Dimethoxypropane

To a suspension of derivative (25) (0.1 g, 0.57 mmol) in dichloromethane (5 mL) containing catalytic amount of *p*-toluenesulfonic acid, was added 2,2-dimethoxypropane (0.14 mL, 1.14 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, dichloromethane (5 mL) was added and the resulting organic layer was washed with 5% aqueous sodium bicarbonate solution and submitted to the "usual work-up," affording an oily residue, which was purified by silica gel column chromatography using a mixture of hexane : isopropanol : pyridine (90 : 9.9 : 0.1 v/v) as eluent, to give (27) in 62% yield, as a colorless oil; ^{1}H NMR (300 MHz): 1.15 (d, 3H, $J = 6.3$ Hz, -CH(O)CH_3), 1.42 (s, 3H, CH_3-a), 1.46 (s, 3H, CH_3-b), 1.53 (ddd, 1H, $J = 4.2$, 7.2 and 15.3 Hz, -C$H_2$$CH_2$OH), 1.91 (dd, 2H, $J = 1.2$ and 7.5 Hz, -CH_2CH=CH_2), 1.96 (m, 1H, -C$H_2$$CH_2$OH), 3.62 (d, 1H, $J = 12.0$ Hz, -CH_2O-), 3.83 (dd, 1H, $J = 1.5$ and 12.3 Hz, -CH_2O-), 3.89 (ddd, 2H, $J = 4.5$, 6.9 and 15.0 Hz, -CH_2CH_2OH), 3.96 (q, 1H, $J = 6.6$ Hz, -CH(O)CH_3), 5.08 (m, 2H, -CH_2CH=CH_2), 5.72 (m, 1H, -CH_2CH=CH_2); ^{13}C NMR (75 MHz): 14.8 (-CH(OH)CH_3), 18.7 (-C(CH_3)$_2$), 29.2 (-CH_2CH=CH_2), 36.3 (-$CH_2$$CH_2$OH), 41.2 (C-5), 59.4 (-$CH_2$$CH_2$OH), 67.4 (-$CH_2$OC($CH_3$)$_2$), 71.8 (-CH(OH)$CH_3$), 98.4 (-C($CH_3$)$_2$), 118.5 (-$CH_2$CH=$CH_2$), 132.4 (-$CH_2$CH=$CH_2$). Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.35; H, 10.43.

Ketalization of (*anti*)-2-Allyl-2-[1′-(1′-hydroxy-ethyl)]-1,4-butanediol (26) with 2,2-Dimethoxypropane

To a suspension of derivative (26) (0.06 g, 0.34 mmol) in dichloromethane (3 mL) containing catalytic amount of *p*-toluenesulfonic acid, was added 2,2-dimethoxypropane (0.08 mL, 0.68 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, dichloromethane (5 mL) was added and the resulting organic layer was washed with 5% aq. sodium bicarbonate solution and submitted to the "usual work-up," affording an oily residue, which was purified by silica gel column chromatography using a mixture of hexane : isopropanol : pyridine (90 : 9.9 : 0.1 v/v) as eluent, to give (28) in 61% yield, as a colorless oil; ^{1}H NMR (300 MHz): 1.10 (d, 3H, $J = 6.6$ Hz, -CH(O)CH_3), 1.40 (s, 3H, CH_3-a), 1.43 (s, 3H, CH_3-b), 1.51 (m, 1H,

-CH_2CH$_2$OH), 1.85 (dt, 1H, $J = 4.8$ and 14.7 Hz, -CH_2CH$_2$OH), 2.04 (ddt, 1H, $J = 1.4$, 7.5 and 15 Hz, -CH_2CH=CH$_2$), 2.65 (ddt, 1H, $J = 1.4$, 7.2 and 14.1 Hz, -CH_2CH=CH$_2$), 3.48 (d, 1H, $J = 11.8$ Hz, -CH_2O-), 3.60 (d, 1H, $J = 12$ Hz, -CH_2O-), 3.83 (m, 2H, -CH$_2$CH_2OH), 4.00 (q, 1H, $J = 6.3$ Hz, -CH(O)CH$_3$), 5.08 (m, 2H, -CH$_2$CH=CH_2), 5.74 (m, 1H, -CH$_2$CH=CH$_2$); ^{13}C NMR (75 MHz): 15.0 (-CH(OH)CH$_3$), 17.3 (-C(CH$_3$)$_2$), 30.8 (-CH$_2$CH=CH$_2$), 34.4 (-CH$_2$CH$_2$OH), 36.7 (C-5), 58.4 (-CH$_2$$CH_2$OH), 66.7 (-$CH_2$OC(CH$_3$)$_2$), 71.8 (-$C$H(OH)CH$_3$), 98.5 (-$C$(CH$_3$)$_2$), 118.1 (-CH$_2$CH=$CH_2$), 133.6 (-CH$_2$$C$H=CH$_2$). Anal. Calcd. for C$_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.30; H, 10.27.

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